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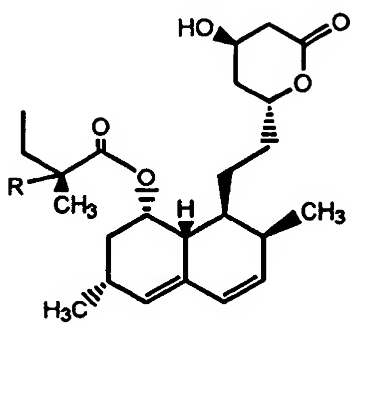
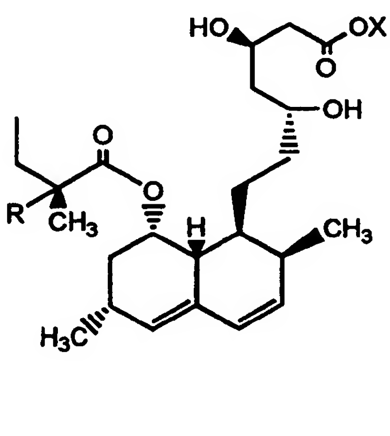
(54) Title: A LACTONIZATION PROCESS



(1)



(2)

(57) Abstract: A process for synthesizing a compound of formula (1) comprising the steps of intramolecular esterification, lactonization, of a compound of formula (2) with a lactonization agent in a suitable solvent thus yielding a reaction medium, wherein R is a hydrogen atom or a lower alkyl group, preferably a methyl group and X is a hydrogen atom or a cation, wherein the lactonization agent forms a hydrated complex with water, released on the lactonization of compound (2) into compound (1), which hydrated complex is substantially insoluble in the solvent.

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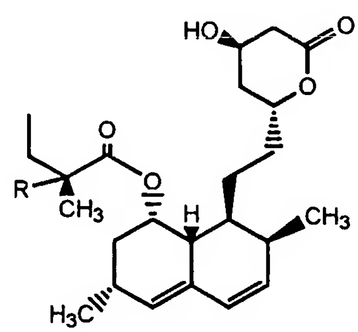
A LACTONIZATION PROCESS

Antihypercholesterolemic compounds lovastatin and simvastatin are widely used in medicine for the lowering of levels of blood cholesterol.

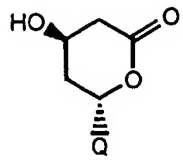
Those compounds are derivatives of mevinic acid and have the following structural formula (1):



(1)

wherein when R = H, the compound is lovastatin and, wherein when R = CH_3 , the compound is simvastatin.

The chemical structure of both compounds is characterised by the presence of a cyclic lactone moiety (4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one group) in the molecule. Accordingly, the chemical structure as expressed by the formula (1) may be simplified by the common formula (A),

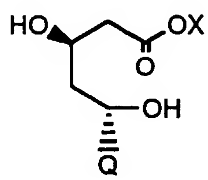


(A)

wherein Q represents the corresponding remaining part of the molecule of lovastatin and simvastatin.

Both compounds may be produced by the fermentation of various microorganisms or they may be prepared synthetically or semi-synthetically by methods known in the art.

Fermentation or synthetic methods for preparing lovastatin or simvastatin usually lead to the formation of a dihydroxyacid form (B) or a salt thereof



(B)

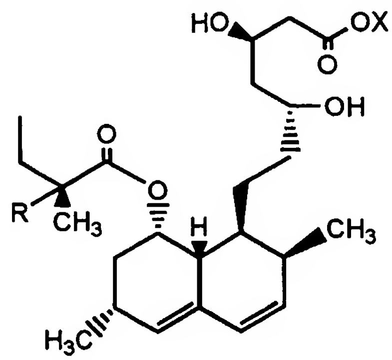
wherein X = H, metal cation, ammonia cation, instead to the desired lactone form (A).

Ammonium salts of the dihydroxyacid form (B) are often used as intermediates in production methods as these salts are nicely crystalline. Acid and lactone forms may also be formed in the mixture.

Whenever this occurs, it is necessary to convert the intermediate dihydroxyacid form (B) (or, accordingly, a salt thereof) into the desired lactone form (A).

Hereafter the dihydroxyacid form (B) of compounds of formula (1) may be denoted as the "statin

acid" or, if appropriate, "lovastatin acid" or "simvastatin acid" of formula (2):



(2)

wherein R and X are as hereinabove defined.

Lactonization is a process wherein a hydroxy acid loses one molecule of water to form an intramolecular ester - a lactone. This reaction is generally catalysed by an acid; the necessary acidity arises either through the ambient acidity of the substrate itself or by addition of a stronger acid, i.e. a lactonization agent to enhance lactonization.

Lactonization is an equilibrium process characterized, in the case of statins, by the following equation:

$$\underset{(B)}{\text{Dihydroxy acid}} \rightleftarrows \underset{(A)}{\text{lactone}} + H_2O$$

In order to obtain a high yield of the lactone, means must be employed to shift the equilibrium to the lactone side of the equation.The common means of shifting the equilibrium to the lactone side from (B) to (A) is

the removal of a reaction product from the reaction mixture.

One known way of removal of the reaction product during lactonization of a statin acid is the physical removal of water produced from the reaction mixture, e.g. by means of azeotropic distillation. In this arrangement, the statin acid and/or ammonium salt thereof is heated in a suitable solvent, for example toluene, butyl acetate, ethyl acetate, cyclohexane to a boiling point thereof, whereby the azeotropic mixture of the solvent and water having a lower boiling point distills off first and the reaction equilibrium is thus shifted to the formation of the lactone. The speed of water and, optionally, ammonia removal may be increased by passing a stream of inert gas through the hot reaction mixture. The ambient acidity of the statin acid is believed to be responsible for the lactonization reaction at these high temperatures.

This process has been disclosed e.g. in US 4444784, US 4582915, US 4820850, US 5159104, WO 98-12188 and many others.

An alternate known possibility (US 5393893) is to perform the lactonization in a two-phase system of an organic solvent, in which the lactone is soluble, and an aqueous acid, whereby the water formed is displaced from the organic layer, containing the lactone, to the aqueous layer.

Both alternatives have the disadvantage that elevated temperatures and long reaction times are necessary to be applied for completing the reaction, whereby statins are sensitive to heating so that impurities may be formed.

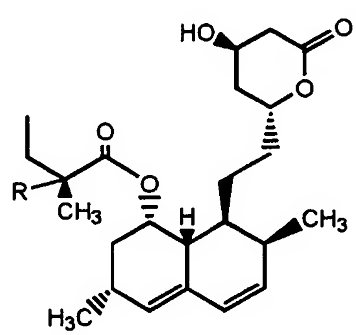
One of the most common impurities arises from dimerization of the starting material. For instance, simvastatin of pharmaceutically acceptable quality (e.g. the quality of Ph.Eur. monograph) should contain only less than 0.2 % of such dimer.

Another known method is based on the removal of the lactone itself from the reaction medium. In this

arrangement, the statin acid or its salt is dissolved in a water-miscible solvent in the presence of an acidic catalyst and water is added to the reaction mixture, after a certain reaction period, as an antisolvent. The lactone is not soluble in water and separates out from the solution, thus shifting the equilibrium in the solution to allow formation of the next lactone. This method has been disclosed in EP 351918 / US 4916239 This reaction does not require elevated temperatures so that the potential for forming impurities, particularly dimers, is lower.

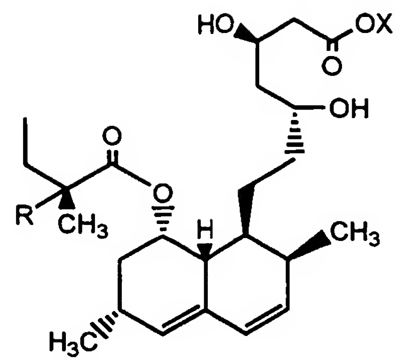
However the selection of the water-miscible solvent and the proper amounts and timings of added water is crucial since fast or premature addition of water can lead to serious problems in isolation of the product as impurities of similar structure present in the starting statin acid may accordingly separate from the solution and decrease the purity of the obtained lactone. In addition, all of the above known lactonization methods require reaction times longer than one hour for obtaining an acceptable degree of conversion. This together with the necessary subsequent work-up, makes these methods complicated to carry out and economically undesirable.

According to a first aspect, the present invention provides a process for synthesizing a compound of formula (1)



(1)

comprising the steps of intramolecular esterification, lactonization, of a compound of formula (2):



(2)

with a lactonization agent in a suitable solvent thus yielding a reaction medium
wherein R is a hydrogen atom or a lower alkyl group, preferably a methyl group and X is a hydrogen atom or a cation,
wherein the lactonization agent forms a hydrated complex with water, released on the lactonization of compound (2) into compound (1), which hydrated complex is substantially insoluble in the solvent.

Optionally, the process also comprises the steps of removal of the hydrated complex after the reaction from the reaction mixture and isolation of the compound (1) from the reaction medium, preferably without an aid of an antisolvent.

This lactonization of the statin proceeds at ambient temperature, is simple and short and is easily operable on an industrial scale.
Furthermore, the process does not require any special techniques or operations for shifting the equilibrium during the reaction.

Preferred aspects of the present invention are also further defined in the claims.

The starting acid form of simvastatin or lovastatin may be employed in a crude or purified state.

A preferred precursor is the ammonium salt of lovastatin or simvastatin acid as this compound may be isolated from reaction mixtures of preceding reaction steps, by methods known per se, in a stable crystalline form. Also this salt form may be used in the crude or purified state.

The reaction solvent employed in the process may be any inert, preferably water immiscible, solvent in which the lactone form is sufficiently soluble.

The starting compound, e.g. the ammonium salt of the statin acid, may, however be only sparingly soluble in the solvent.

In a particularly advantageous embodiment, the acidic compound and the chemically converted acidic compound, i.e. the stable hydrated complex, are also essentially insoluble in the solvent and may thus be easily removed from the reaction mixture by filtration after termination of the lactonization reaction.

The solvent employed is preferably anhydrous. Suitable solvents are e.g. hydrocarbons such as benzene or chlorinated hydrocarbons such as dichloromethane.

The lactonization agent is, in general, an organic or inorganic compound, preferably of acid nature, which is able to bind water and, if applicable, the cation or ammonia.

A preferred lactonization agent is anhydrous methane sulfonic acid. Methane sulfonic acid is able to bind water to form a hydrate and is also able to bind ammonia if the ammonium salt of a statin is used.

The hydrated complex carrying the entrapped water and ammonia is preferably substantially insoluble in the reaction solvent.

Phosphorous pentoxide, a strongly acidic ion-exchange resin (such as Dowex 50X2 - 400), molecular sieves, acid clay or acidic silica gel are further examples of suitable acidic lactonization agents to bind water and/or ammonia into insoluble compounds. Ion exchange acidic resins are particularly advantageous as they may work in various types of solvents, including polar solvents such as actonitrile, are easily removable

from the reaction mixture after the reaction and may be easily regenerated by conventional procedures. Care is to be taken that the resins are sufficiently dry prior to use.

If the lactonization agent, e.g. ion-exchange resin, molecular sieve, clay or silica gel is not sufficiently acidic by its nature, it may be combined with necessary amount of an acid directly in the reaction mixture.

The amount of the lactonization agent to be employed may vary depending on the nature of the lactonization agent and the starting material.
If the ammonium (or another) salt of the statin acid is used, one acid equivalent of the agent is spent to bind the salt cation; the same or next equivalent is necessary to bind water. Preferably, slightly more than the stoechiometric equivalent of the agent is required, as the molar excess of the acidic compound serves for catalysis of the reaction. E.g., a suitable amount of methane sulfonic acid in relation to simvastatin or lovastatin acid ammonium salt is 1-50% molar excess (1.01-1.5 equivalents), while phosphorous pentoxide requires about 50% stoechiometric excess.
The reaction temperature of the process is essentially ambient. The mixture of the starting acid or salt is stirred, preferably under a nitrogen atmosphere, together with the lactonization agent without heating or cooling. No control of the reaction temperature is generally required.

Progress of the reaction may be monitored by any suitable method allowing separation and determination of the amounts of the starting and formed product in the reaction mixture. Such a suitable method is high performance liquid chromatography (HPLC).

The lactonization process proceeds with a high conversion rate; whereby a sufficient conversion (more than 90% and more preferably than 95%) at ambient temperature may be obtained in 15-60 minutes.

For example, after stirring one molar

equivalent of ammonium salt of simvastatin acid with 1.3 molar equivalents of anhydrous methane sulfonic acid in dichloromethane at ambient temperature, 85% conversion was observed by HPLC after 5 minutes and 94% conversion was accordingly reached in 15 minutes.

With phosphorous pentoxide, the complete conversion may be reached in 3 hours at ambient temperature.

A strongly acidic ion exchange resin requires the same and sometimes longer reaction times at ambient temperature. For instance, Dowex 50X2-400 resin provided 95% conversion in 2 hours in acetonitrile, while in dichloromethane the reaction required about 24 hours for obtaining complete conversion at ambient temperature. A shorter reaction time may be obtained by increasing the reaction temperature, e.g. up to 50°C, whereby the amounts of the undesired by-products, particularly the dimer, are still negligible.

As the reaction temperature is mild and the reaction time is short, the potential for forming impurities is low. The HPLC confirmed that the dimeric impurity was formed in amounts less than 0.1 mass % under the conditions referred to above. Other types of impurities, for instance products of elimination of the OH-group, are also only formed in negligible amounts.

Insoluble polymeric lactonization agents, e.g. acidic ion-exchange resins may also be employed within the process of our invention in a continual or semicontinual reactor. For instance, the solution of the substrate may be passed or circulated through a column filled with the resin until the sufficient conversion is obtained. The solution comprising the lactonized statin is then elaborated to isolate the statin. This may lead to economic use of the resin and, as well, regeneration of the resin may be simple.

Isolation of the statin from the reaction medium after lactonization is also simple and does not require any contrasolvent to precipitate the statin. In the case of insoluble acidic lactonization agents such

as ion-exchange resin, its excess (incl. the spent part of such compound that binds water and /or ammonia) is simply removed by filtration.

Alternately, the remaining excess of the acidic compound can be firstly neutralized by a suitable amount of a base, whereby preferably, organic amines such as triethylamine or pyridine are employed, as such compounds do not react with the acid catalyst with formation of water.

The insoluble neutralized acidic compound is subsequently removed from the reaction mixture by filtration or centrifugation.

Water soluble co-products carrying the bound water or ammonia may alternately be removed from the reaction mixture by extraction with alkalinized water. The remaining solution comprises the formed lactone.

The desired statin may be obtained by crystallization after cooling, optionally after concentration of the solution, or by evaporation of the solution to dryness, yielding the corresponding statin in a solid state.

Crude statin obtained by this process may optionally be subsequently purified to a desired degree of purity by any suitable conventional purification method known per se. E.g., it may be crystallized from a solvent system or may be chromatographed on a suitable carrier.

Statins produced by the process of the present invention, e.g. simvastatin, may further be used in the production of pharmaceutical compositions useful in treatment of various types of hypercholesterolemia. They may be formulated into e.g. tablets or capsules comprising therapeutically effective amounts of the active substance together with pharmaceutically acceptable carriers or diluents. The formulation methods may comprise various techniques of blending, filing and/or compressing known in the art.

Examples

Example 1

Lactonization of ammonium salt of simvastatin by methane sulfonic acid

A 100 ml three-necked flask equipped with a $CaCl_2$ tube, stirring bar and a nitrogen inlet was charged with 2.5 g of simvastatin ammonium salt, 30 ml of dichloromethane and 690 mg of anhydrous methane sulfonic acid (1.3 molar equivalent). The resulting suspension was stirred at room temperature under a nitrogen atmosphere for 15 minutes. Then, 170 mg of triethylamine was added and after 10 minutes of stirring the solid was filtered off. The clear solution was evaporated to dryness. The rest after evaporation was dissolved in 21 ml of ethanol/water (1:1 v/v) mixture under elevated temperature and crystallized by subsequent leaving overnight at room temperature. The precipitated solid was filtered off and washed with a small amount of the same ethanol/water mixture. Yield of simvastatin after drying: 1.8 g (80%).

The crude product (1g) was recrystallized to obtain 0.82 g of pure simvastatin with dimer content 0.1mass% (HPLC).

Example 2

Lactonization of ammonium salt of simvastatin by phosphorus pentoxide

A 100 ml flask equipped with $CaCl_2$ tube, stirring bar and nitrogen inlet was charged with 2.5 g of simvastatin ammonium salt and 30 ml of dichloromethane. To the stirred mixture, 1.17g of phosphorus pentoxide was added in one portion. The resulting suspension was stirred at room temperature under nitrogen. After complete conversion (HPLC), the reaction mixture was treated with 5% solution of $NaHCO_3$ and extracted with 3x100 ml of ethyl acetate. The organic layer was washed with water, dried by magnesium sulfate and the solvent was removed in vacuo to yield 1.67g of simvastatin . The

product was recrystalized in 62% yield and dimer content 0.08% (HPLC).

Example 3
Lactonization of ammonium salt of simvastatin by ion-exchange resin

A) Dowex 50X2-400 resin was washed with water, methanol and ether and dried at 70C. 2.5 g of simvastatin ammonium salt was suspended in 50 ml of dichloromethane under nitrogen and 2.5 g of the pre-dried Dowex resin was added. The mixture was stirred at room temperature. After two days the resin was removed by filtration and washed with dichloromethane. The combined filtrates were evaporated at reduced pressure to obtain 2.31 g of a white solid. The product was recrystallized in 82% yield. Dimer content 0.06%.

B) The above experiment was repeated using acetonitrile as a solvent. After 2 hours, the HPLC analysis of the reaction mixture shown 95% conversion. The reaction was terminated after 6 hours and elaborated as above to obtain simvastatin as white crystals in 95% yield and of 99% purity by HPLC (dimer content 0.05%). After recrystallization from ethanol/water, the purity increased to 99.5%.

C) The above experiment B) was repeated, but the reaction temperature was increased to 50°C. The reaction was terminated after 4 hours and elaborated as above to obtain simvastatin as a sticky solid mass. After crystalization, simvastatin with 99.3% purity (HPLC) was obtained.

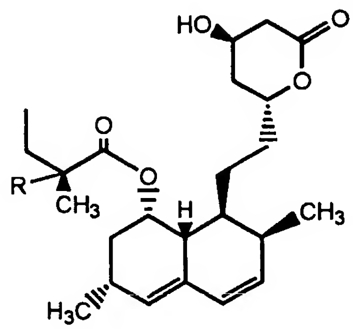
Example 4
Lactonization of simvastatin acid by phosphorus pentoxide

A 100 ml flask equipped with CaCl2 tube, stirring bar and nitrogen inlet was charged with 2.4 g of simvastatin acid and 30 ml of dichloromethane. To the stirred mixture, 1.17g of phosphorus pentoxide was added in one portion. The resulting suspension was stirred at room temperature under nitrogen. After complete

conversion (HPLC), the reaction mixture was treated with 5% solution of $NaHCO_3$ and extracted with 3x100 ml of ethyl acetate. The organic layer was washed with water, dried by magnesium sulfate and the solvent was removed in vacuo. The rest was dissolved in 12 ml of toluene, 40.5 ml of cyclohexane was added and the mixture was heated until a clear solution was obtained. The solution was stored overnight at room temperature, the precipitated crystals were filtered off, washed with cyclohexane and dried to give 1.95 g of simvastatin.

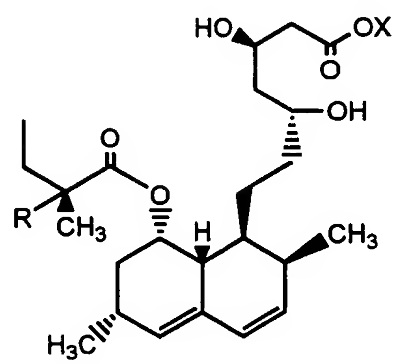
CLAIMS

1.A process for synthesizing a compound of formula (1)



(1)

comprising the steps of intramolecular esterification, lactonization, of a compound of formula (2):



(2)

with a lactonization agent in a suitable solvent thus yielding a reaction medium
wherein R is a hydrogen atom or a lower alkyl group, preferably a methyl group and X is a hydrogen atom or a cation,

wherein the lactonization agent forms a hydrated complex with water, released on the lactonization of compound (2) into compound (1), which hydrated complex is substantially insoluble in the solvent.

2. Process according to claim 1 wherein compound (2) is subsequently isolated from the reaction medium, and wherein compound (1) is preferably, substantially soluble in the solvent.

3. Process according to claims 1 or 2 wherein X is a hydrogen atom, a metal cation or an ammonium cation.

4. Process according to any of the preceding claims wherein the solvent is substantially inert.

5. Process according to any of the preceding claims wherein the solvent is substantially immiscible in water.

6. Process according to any of the preceding claims wherein the solvent is a hydrocarbon solvent or a halogenated hydrocarbon or mixtures thereof.

7. Process according to any of the preceding claims wherein the solvent is a halogenated hydrocarbon solvent, preferably a chlorinated hydrocarbon solvent, most preferably being dichloromethane.

8. Process according to any of the preceding claims wherein the lactonization agent is an acidic compound.

9. Process according to any of the preceding claims wherein the lactonization agent is substantially anhydrous.

10. Process according to any of the preceding claims wherein the lactonization agent is selected from one or more of the following: methane sulphonic acid, phosphorus pentoxide, a strongly acidic ion-exchange resin.

11. Process according to any of the preceding claims wherein the lactonization agent is methane sulphonic acid and/or a strongly acidic ion-exchange resin.

12. Process according to any of the preceding claims wherein the lactonization agent binds ammonia upon

forming the hydrated complex.

13. Process according to any of the preceding claims wherein the hydrated complex is removed from the reaction medium, preferably in a substantially solid form by means of filtration.

14. Process according to claim 13 wherein before the filtration step a base, preferably an organic amine, such as triethylamine and/or pyridine, preferably triethylamine is added to the reaction medium.

15. Process according to claims 1-13 wherein the hydrated complex is removed from the reaction medium by means of extraction with alkalinized water.

16. Process according to any of the preceding claims wherein isolation of compound (1) is carried out without an aid of an antisolvent.

17. Process according to any of the preceding claims 2-16 wherein compound (1) is isolated from the reaction medium by crystallization or by evaporation of the reaction medium to dryness.

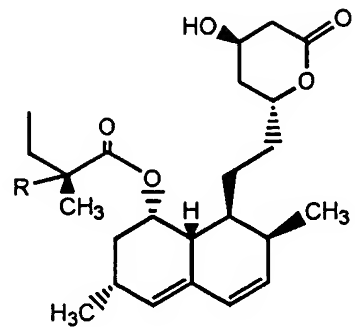
18. Process according to any of the preceding claims wherein the compound of formula (2) is the ammonium salt of simvastatin acid.

19. Process according to any of the preceding claims wherein the molar ratio between compound (2) and the lactonization agent is roughly 1:1.01 to 1:1.5.

20. Process according to any of the preceding claims wherein lactonization of compound (2) proceeds without heating the reaction medium.

21. Process according to any of the preceding claims wherein lactonization of compound (2) has a reaction time of between 15 and 60 minutes.

22. A compound of formula (1):



(I)

wherein R is a hydrogen atom or a methyl group, obtainable according to any of the preceding claims.

23. A pharmaceutical composition comprising a compound of formula (1) according to claim 22.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 02/00161

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D309/30 A61K31/366 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 00606 A (KANEKA CORP.) 4 January 2001 (2001-01-04) the whole document -& EP 1 110 959 A (KANEKA) 27 June 2001 (2001-06-27) ---	1-6,8-22
A	EP 0 351 918 A (MERCK) 17 July 1989 (1989-07-17) cited in the application page 1 -page 7	1,10,11
X	page 1 -page 3 ---	22,23
A	EP 0 511 867 A (MERCK) 4 November 1992 (1992-11-04) cited in the application page 1 -page 9 ---	1,9,18, 20-23

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
30 May 2002	06/06/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 01 44144 A (RANBAXY) 21 June 2001 (2001-06-21) page 1 -page 10	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ınal Application No
PCT/NL 02/00161

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